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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/835,082	04/12/2001	Mark J. Ratain	ARCD:374US/GNS	3017

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EXAMINER
WILDER, CYNTHIA B

ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 08/28/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/835,082	RATAIN ET AL.	
	Examiner	Art Unit	
	Cynthia B Wilder	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 July 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *77-84 and 88-97* is/are pending in the application.

4a) Of the above claim(s) *95-97* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *77-84 and 88-94* is/are rejected.

7)☒ Claim(s) *80 and 81* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 April 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Detailed Action* .

DETAILED ACTION

1. This case has been transferred from the previous Examiner J.C. Einsmann in Art Unit 1634 to Examiner Cynthia Wilder in Art Unit 1637. Applicant may contact the Examiner via the contact information recited at the bottom of this action.

Election/Restriction

2. Applicant's election with traverse of claims 77-84 and 88-97 and species election of ABCG2 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that the species election in improper because ABC transporters have common functional features. This is not found persuasive because Applicant has not identified any similar functional features of the different ABC transporters listed in the claims. While some of the different transporter may have similar structure features, the ABC transporter do not all have similar functional features as Applicant contends. For example, CFTR(cystic fibrosis transmembrane conductance regulator) which is member of the ABC transporter superfamily is a cyclic AMP chloride channel. Mutation in the CFTR results in failure to secrete chloride and thus results in cystic fibrosis. MDR (multi-drug resistance) which is a member of the ABC transporter superfamily accounts for much of the drug resistance that occurs in cancer treated patients. Claims 95-97 have been withdrawn from prosecution as being drawn to a non-elected invention. Claims 77-84 and 88-94 are discussed below.

The requirement is still deemed proper and is therefore made FINAL.

Objections

3. The specification is objected to because the specification contains sequences (primers) at page 113 that are not listed in the sequence listing or CRF and are not represented by a sequence identifier (SEQ ID NO:). Appropriate correction is required.

4. Claims 80 and 81 are objected to because the sequence identifiers are incorrect. It is suggested changing SEQ. ID. NO. 1 and SEQ. ID. NO. 3 to SEQ ID NO:1 and SEQ ID NO: 3.

Claim Rejections - 35 USC § 112 first paragraph: Lack of Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 77-84 and 88-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether the necessary experimentation is undue (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include, but are not limited to:

I. Quality of Experimentation Necessary

The claimed invention is drawn to a method for evaluating the risk of flavopiridol-induced toxicity in a patient comprising evaluating a UGT1A9-encoding nucleic acid or a ABC-encoding nucleic acid of the patient for a polymorphism. The specification beginning at page 97 discloses well known nucleic acid detection methods for identifying single nucleotide polymorphisms (SNPs). At page 113, the specification discloses a method for identifying a region containing a SCA2-SNP using PCR amplification procedures. The specification however fails to identify what the SCA2-SNP is or how the SCA2-relates to the method of evaluating the risk of flavopiridol-induced toxicity. In fact, the specification fails to identify or disclose any SNP or polymorphism associated with flavopiridol-induced toxicity. There is no disclosure describing the association of one single SNP or polymorphism to UGT1A9 or to an ABC-encoding nucleic acid. There is no disclosure anywhere in the specification wherein a specific polymorphism is linked to the risk of flavopiridol-induced toxicity. There is no information provided to enable one of ordinary skill in the art to make or use the claimed method as described to evaluate the risk of flavopiridol-induced toxicity since no polymorphisms of the AGT1A9- or ABC-encoding nucleic acid have been identified as it relates to flavopiridol. There is no information to allow one of ordinary skill in the art to make or use the claimed method using the large number of undisclosed polymorphic sequences. As to the quality of experimentation required, one of skill in the art would have to design an experimental procedure to evaluate the risk of flavopiridol-induced toxicity in a patient and to identify polymorphisms of a UGT1A9 or ABC nucleic acid as they relate to flavopiridol.

II. Amount of Direction and Guidance and Presence or Absence of Working Examples

The specification does not provide a method of evaluating the risk of flavopiridol-induced toxicity that bears a reasonable correlation to the entire scope of the claims. The example starting at page 118 does not describe or disclose a single polymorphism that is associated with any nucleic acid or is associated with flavopiridol. The examples merely teach patient treatment with a flavopiridol compound, pharmacokinetics for quantitating flavopiridol in plasma using HPLC or metabolism of flavopiridol and statistical analysis. Example 3 suggest pharmacogenetic screening and polymophism analysis but does not describe or disclose how the polymorphic analysis occurs or detection of any polymorphism. There is no indication from the specification wherein a polymorphism is responsible for flavopiridol-induced toxicity in any patient or animal. No example is given wherein a polymorphism of the UGT1A9 -encoding nucleic acid is detected or wherein a polymorphism of the ABC-encoding nucleic acid is detected wherein the polymorphism is associated with the risk of flavopiridol-induced toxicity. Merely, making reference to polymorphisms of the UGT1A9-encoding nucleic acid and/or the ABC-encoding nucleic acid being associated with flavopiridol induced toxicity does not enable one skill in the art to use the instant invention as claimed. Clearly, the claimed invention provides insufficient guidance and direction and lacks proper working examples for one skilled in the art to make and use the claimed invention without undue experimentation.

III. Nature of the Invention

The nature of the invention is a method for evaluating the risk of flavopiridol-induced toxicity in a patient comprising evaluating a UGT1A9-encoding nucleic acid or ABC-encoding

nucleic acid of a patient for a polymorphism. The specification however does not define any polymorphisms of the UGT1A9-encoding nucleic acid or the ABC-encoding nucleic acid. While the specification discloses a SCA2-SNP at page 113, the specification does not disclose or describe what the SNP is or how the SNP relates to the instant invention. To reiterate, merely making reference to methods for detecting SNPs does not enable a person to evaluate the risk of flavopiridol-induced toxicity by evaluating a UGT1A9-encoding nucleic acid or ABC-encoding nucleic acid for a polymorphism. Furthermore, identifying a polymorphism in a UGT1A9-encoding or ABC-encoding nucleic acid does not necessarily equate to detecting or evaluating toxicity associated with flavopiridol because some polymorphisms may simply be non-functional or silent mutations. Thus further experimentation is required.

IV. Relative skill in art and predictability of the art

The level of skill in molecular biology at the time the invention was made is high, however the level of unpredictability in molecular biology is also high. Although certain relevant techniques useful to the claimed invention were know in the prior art, the prior art does not teach a method for detecting or evaluating the risk of flavopiridol-induced toxicity in a patient by evaluating a UGT1A9-encoding nucleic acid for a polymorphism or by evaluating a ABC-encoding nucleic acid for a polymorphism.

For all of the forgoing reasons, undue experimentation is necessary for one of skill in the art to obtain the claimed invention.

Claim Rejections - 35 USC § 112 first paragraph: Lack of Adequate Written Description

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 77-84 and 88-94 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claimed invention is drawn to a method for evaluating the risk of flavopiridol-induced toxicity in a patient comprising evaluating a UGT1A9-encoding nucleic acid of the patient for a polymorphism. The claimed invention is also drawn to method for evaluating the risk of flavopiridol-induced toxicity in a patient comprising evaluating a ABC-encoding nucleic acid of the patient for a polymorphism. The disclosure of evaluating a UGT1A9-encoding nucleic acid or ABC-encoding nucleic acid for a polymorphism encompasses a large number of nucleic acid species not describe or disclosed anywhere in the specification. A representative number of species for each genus must be disclosed to meet the written description requirement of 112, first paragraph. As set forth by the Court in *Vas Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, the written description must convey to one of skill in the art "with reasonable clarity" that as of the filing date Applicant was in possession of the claimed invention. Absent a written description disclosing a representative number of the species as claimed in claims 77-84 and 88-94

of the specification fails to show that Applicant was, in fact, "in possession of the claimed invention" at the time the application for patent was filed.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the Applicant regards as his invention.

10. Claim 77-84 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claims 77-84 and 88-94 are incomplete and indefinite in claim 77 because it cannot be determined how evaluating a UGT1A9-encoding nucleic acid or ABC-encoding nucleic acid for a polymorphism relates to evaluating the risk of flavopiridol-induced toxicity. Additionally the term "evaluating" is a non-specific activity and therefore it is unclear how the claimed method operates to detect the polymorphism". Method claims need not recite all operating details but should at least recite positive, active steps so that the claims will set out and circumscribe a particular area with a reasonable degree of precision and particularity and make clear what subject matter that claims encompass as well as make clear the subject matter from which other would be precluded. *Ex parte Erlich*, 3 USPQ2d 1011 at 6. It is suggested amending the claims at step (a) to recite positive and active method steps.

(b) Claims 77-84 and 88-94 are indefinite for the abbreviations "UGT1A9", "ABC", "ABCG2" and "BCRP1" because abbreviations often have more than one meaning in the art. It is suggested inserting the full name of the abbreviations into the claim.

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Cynthia Wilder whose telephone number is (703) 305-1680. The examiner can normally be reached on Monday through Thursday from 7:00 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion, can be reached at (703) 308-1119. The official fax phone number for the Group is (703) 308-4242. The unofficial fax number is (703) 308-8724.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group's Patent Analyst, Monica Graves at (703) 305-3002 or Group's receptionist at (703) 308-0196.

Cynthia B. Wilder, Ph.D.

August 22, 2002

KENNETH R. HORLICK, PH.D
PRIMARY EXAMINER
8/26/02